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REVIEW ARTICLE

Should we give thromboprophylaxis to patients with liver cirrhosis and coagulopathy?

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Abstract

Patients with liver cirrhosis are characterized by decreased synthesis of both pro- and anticoagulant factors, and recently there has been evidence of normal generation of thrombin resulting in a near normal haemostatic balance. Although it is generally recognized that bleeding is the most common clinical manifestation as a result of decreased platelet function and number, diminished clotting factors and excessive fibrinolysis, hypercoagulability may play an under recognized but important role in many aspects of chronic liver disease. In fact, they can encounter thrombotic complications such as portal vein thrombosis, occlusion of small intrahepatic vein branches and deep vein thrombosis (DVT). In particular, patients with cirrhosis appear to have a higher incidence of unprovoked DVT and pulmonary embolism (PE) compared with the general population. In dedicated studies, the incidence of DVT/PE ranges from 0.5% to 1.9%, similar to patients without comorbidities, but lower than patients with other chronic diseases (i.e, renal or heart disease). Surprisingly, standard coagulation laboratory parameters are not associated with a risk of developing DVT/PE; however, with multivariate analysis, serum albumin level was independently associated with the occurrence of thrombosis. Moreover, patients with chronic liver disease share the same risk factors as the general population for DVT/PE, and specifically, liver resection can unbalance the haemostatic equilibrium towards a hypercoagulable state. Current guidelines on antithrombotic prophylaxis do not specifically comment on the cirrhotic population as a result of the perceived risk of bleeding complications but the cirrhotic patient should not be considered as an auto-anticoagulated patient. Therefore, thromboprophylaxis should be recommended in patients with liver cirrhosis at least when exposed to high-risk conditions for thrombotic complications. Low molecular weight heparins (LWMHs) seem to be relatively safe in this group of patients; however, when important risk factors for bleeding are present, graduated compression stockings or intermittent pneumatic compression should be considered.

Keywords

thrombosis, liver cirrhosis

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Introduction

The liver plays several key roles in blood coagulation and is involved in both primary and secondary haemostasis.[1,2] Hepatocytes are the site of synthesis of all coagulation factors and their inhibitors except for von Willebrand factor.[3]

Liver damage is commonly associated with impairment of coagulation, when hepatic reserve is poor. The haemostatic system is in a delicate balance between prothrombotic and antithrombotic processes, aiming to prevent excessive blood loss from injured vessels and to prevent spontaneous thrombosis. Liver failure is accompanied by multiple changes in the haemostatic

system, because of reduced plasma levels of procoagulant and anticoagulant clotting factors synthesized by hepatocytes and sinusoidal cells.[4,5] Therefore the clinical result (thrombosis or bleeding) depends on the derangement in the balance of these complex mechanisms.

Although it is generally recognized that bleeding is the most common clinical manifestation as a result of decreased platelet function and number, diminished clotting factors and excessive fibrinolysis, hypercoagulability may have a poorly appreciated but important role in many aspects of chronic liver disease.

Clinically, thrombotic complications can be observed in patients with cirrhosis, despite standard coagulation laboratory tests revealing a prolonged PT/INR, which is perceived normally to be indicative of a bleeding tendency.[6] Portal vein thrombosis (PVT) is a common complication of liver cirrhosis, with an incidence of about 10–15%, and probably as a result of multiple local and systemic factors including a (relative) hypercoagulable state.[7] Genetic prothrombotic predisposition is found in about 70% of patients with PVT, compared with 8% in those without.[8,9]

It is also known that coagulation disorders associated with chronic liver disease, especially in liver cirrhosis, can promote further liver damage. Wanless and colleagues have clearly demonstrated histopathological evidence of secondary hepatic damage as a result of thrombosis and occlusion of intrahepatic venous blood vessels.[10] Moreover there is evidence from both clinical observations and animal studies suggesting that a hypercoagulable and hypofibrinolytic state can promote liver fibrosis.[11]

During the concomitant presence of portopulmonary syndrome and portal hypertension, the local procoagulant state contributes to the obliterative arteriopathy in cirrhotic patients with this complication.[12]

Moreover, the risk of DVT and PE is not well documented in cirrhotic patients, yet is reported.[13] A summary of thrombotic conditions that can occur in patients with liver disease with corresponding aetiological factors is represented in Table 1. Based on this clinical evidence, the patient with cirrhosis cannot be considered to be protected from thrombotic risk as a result of auto-anticoagulation.

Laboratory evaluation of coagulation in patients with liver disease shows normal thrombin generation in platelet poor and platelet rich plasma, given a platelet count greater than 80 000/μl.[14] Similarly, thromboelastography showed no differences in coagulation parameters in cirrhotic patients compared with healthy controls.[15]

Standard laboratory tests are not useful in evaluating the coagulation status in patients with chronic liver disease. The prothrombin time does not portray adequately the *in vivo* haemostatic status in patients with liver disease, as the test is only sensitive for procoagulant factors. For this reason, liver disease patients with a prolonged PT can have normal thrombin generation, as anticoagulant factors are also deficient in these patients. Moreover, the international normalized ratio (INR) has been shown to be an inconsistent tool in this group of patients, as there may be substantial variation from one laboratory to another in the INR of a single patient[16] using different thromboplastins, which are calibrated with methods likely unsuitable for cirrhotic patients.

Table 1 Evidences of thrombotic events and aetiologies' in patients with liver diseases

Portal vein thrombosis	Local factor (flow obstruction)
	Inflammation
	Systemic prothrombotic conditions
Deep vein thrombosis and pulmonary embolism	Decrease synthesis of anticoagulant factors
	Systemic increase of proinflammatory cytokines
Progression of cirrhosis by parenchymal microvascular thrombosis	Parenchymal extinction
Extracorporeal circuit thrombosis	Mechanical obstruction
	Inflammation
	Contact activation of coagulation cascade
Pulmonary hypertension	Endothelial dysfunction (shear stress)
	Microvascular thrombosis
Metabolic syndrome and NASH	Atherosclerosis
	Increased systemic inflammation
	Increased procoagulant factor levels correlated to insulin resistance

Incidence of DVT and PE in patients with liver cirrhosis

Venous thromboembolism (VTE) is a major national health problem, with at least 200 000 new cases per year in the United States and an incidence of 74.5 per 100 000 persons per year in the United Kingdom. Prevention is essential to reduce the incidence of VTE and the subsequent high risk of mortality. Endogenous coagulopathy in hospitalized cirrhotic patients is often considered to be protective against pulmonary thromboembolism and DVT despite the lack of empirical data to confirm this hypothesis.

In a small case–control study from United States, Heit and colleagues found a substantially reduced relative risk of 0.1 of VTE in patients with serious liver disease.[17] On the other hand, a recent case–control study from the United Kingdom showed a non-significant increased relative risk of 1.7 of VTE in patients with chronic liver disease.[18] However, these two studies were not properly designed to evaluate the incidence of VTE in patients with cirrhosis.

A nationwide population-based study undertaken in Denmark, which evaluated more than 99 000 patients with thromboembolism, showed that patients with chronic liver disease are at greater risk of VTE ranging from 1.7 to 1.9 in patients with cirrhotic and non-cirrhotic liver disease, respectively.[19] In this study, a subanalysis evaluating the risk of unprovoked VTE (occurrence of VTE 90 days after any risk factor) revealed that cirrhosis and liver

Table 2 Incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients with liver cirrhosis in published studies

Author	Type of study	Numer of patients analyzed	Incidence of DVT/PE	% of patients thromboprophylaxis	DVT number (%)	PE number (%)	DVT+PE number (%)
Northup *et al.* (2006)[13]	Case–control	21.000	113 (0.5%)	21% (7% on medical prophylaxis)	74 (65.5%)	22 (19.5%)	17 (15%)
Garcia-Fuster *et al.* (2008)[21]	Retrospective	2074	17 (0.8%)	NA	10 (59%)	6 (35%)	1 (6%)
Gulley *et al.* (2008)[20]	Case–control	963	18 (1.87%)	0%	NA	NA	NA

disease carry an even greater risk of VTE with an odds ratio (OR) of 2.1 and 3.6 if age is less than 55 years. Interestingly, the authors also found that the relative risk (RR) for VTE was similarly elevated in a sub-analysis of patients with hepatocellular carcinoma within the group of patients with cirrhosis (RR 1.8).[19] However, this population-based study had no information on patient characteristics or the severity of liver disease.

To date, three studies have been published which aimed to investigate specifically the prevalence of DVT and PE in patients with liver cirrhosis, two case–control studies[13,20] and one retrospective study[21] in three different institutions.

Overall, 24 037 cirrhotic patients and 12 518 controls (including 113 cirrhotic patients without DVT) were studied and the incidence of DVT or PE ranged from 0.5% to 1.9% across the different studies. In particular, in the larger population evaluated (which was the one with the lower incidence) 21% of patients received antithrombotic prophylaxis with drugs (7%) or compression devices (14%) at the time they experienced the thrombotic event.[13] Thus, even patients with a prolonged PT who receive antithrombotic drugs can develop a venous thrombosis.

Gulley *et al.* performed a matched analysis showing that patients with cirrhosis did have a similarly increased risk of PVT compared with non-cirrhotic patients without comorbidities; however, the risk of developing DVT/PE was low when compared with patients matched for morbidity and risk index (ie subjects with chronic renal failure).[20]

A summary of the three cohort studies dedicated to evaluate the incidence of DVT/PE in cirrhotic patients is represented in Table 2.

Role of the aetiology of liver disease as a risk factor for the development of DVT/PE

Northup and colleagues are the only group to have analysed the role of liver disease aetiology as a risk factor for DVT/PE, but they did not demonstrate any difference in the incidence of VTE in patients with different aetiologies.[13] However, patients with autoimmune liver disease have been shown to have a higher incidence of portal vein thrombosis compared with other aetiologies[22] and patients with cholestatic liver disease are characterized by a hypercoagulable state as evidenced by thromboelastography (TEG) in about 50% of cases.[23] Moreover, patients with cholestatic aetiology of liver disease were characterized as having enhanced thrombin generation as estimated by TEG at baseline before liver transplantation compared with non-cholestatic cirrhotics.[24]

This hypercoagulable state can be seen as increased platelet activation visible on the TEG trace.[23] A further experimental study has demonstrated hyperactivation of platelets in patients with cholestatic liver disease compared with other aetiologies of cirrhosis. This may be as a result of the effect of chronic exposure to high levels of bilirubin which can increase platelet adhesion.[25] Moreover, increased levels of von Willebrand factor have been described in cholestatic liver diseases.[25]

In accordance with these findings, patients with cholestatic liver disease show less bleeding and less fibrinolysis during liver transplantation;[5,24] however, a study by Northup did not show a higher incidence of thromboembolic complications in this group.[13]

Moreover, Sogard and colleagues pointed out that even patients with non-cirrhotic liver disease are at greater risk of DVT/PE occurrence. This can be because of the high prevalence of additional risk factors such as obesity and diabetes amongst this category of patients of non-alcoholic liver disease.[19] The metabolic syndrome and non-alcoholic fatty liver disease have been associated with a greater risk of atherosclerosis and endothelial dysfunction which are thought to contribute to the prothrombotic state.[26] Furthermore, insulin resistance correlates with increased platelet adhesion, increased tissue factor and factor VII, and hypofibrinolysis as a result of high PAI-1 levels.[27]

Finally, patients with hepatocellular carcinoma are known to be at greater risk of thromboembolic complications (i.e. portal vein thrombosis and PE), and increased levels of thrombin–antithrombin complexes have been demonstrated.[28]

Risk factors for the development of DVT/PE in patients with liver cirrhosis

Surprisingly, standard coagulation laboratory parameters are not associated with the risk of developing DVT/PE. In particular, INR was not associated with thrombosis risk in the multivariate analyses of Gulley *et al.*[20] and Northup *et al.*[13] and the mean INR value in cirrhotic patients with DVT was similar to those of the two other studies in the study of Garcia-Fuster and colleagues.[21] This reinforces the notion that the perceived coagulopathy in patients with liver disease, as reflected in prolonged INR values, does not protect patients against venous thrombosis.

Multivariate analysis to analyse risk factors for the development of thrombosis was performed in two of the three dedicated studies.[13,20] Serum albumin level was independently associated with the occurrence of thrombosis in both of them. In the study by Gulley *et al.*, the mean albumin level in cirrhotic patients with DVT was 2.7 ± 0.6 g/dl., similar to mean serum levels in cirrhotic patients with DVT in the retrospective series in Spain and USA.

Although the severity of liver disease assessed by Child–Pugh and model for end-stage liver disease (MELD) scores was not directly correlated with the risk of developing thromboembolic complications, the evidence of the link with decreased hepatic synthetic function as reflected by albumin levels is in keeping with the hypothesis that the concomitant reduction of pro- and anticoagulant factors (antithrombin, protein C and S) can reset the balance to a new precarious equilibrium which can be easily disturbed.

Patients with cirrhosis and DVT/PE may share the same risk factors as other non-cirrhotic patients with thrombotic complications such as venous stasis, infection, congestive heart failure, acute respiratory disease and immobilization.[20] Surgery and, in particular, orthopaedic surgery is one of the major risk factors for VTE in cirrhotic patients. In the cirrhotic patient, liver resection such as for hepatocellular carcinoma has been shown to correlate with a higher incidence of thrombotic complications (PE 7% in 127 living donors). It is correlated with a prothrombotic state when evaluated by TEG up to 10 days after surgery despite antithrombotic prophylaxis with Low molecular weight heparin (LWMH).[29] In fact, during hepatic resection, thrombin–antithrombin complexes are elevated and this effect can be seen up to the 7th day after surgery as a hypofibrinolytic state, even during thromboprophylaxis with LMWH.[30]

Thrombotic prophylaxis in patients with liver cirrhosis

Current guidelines on antithrombotic prophylaxis do not specifically comment on the cirrhotic population.[31] Despite a lack of specific guidelines, there has been a reduction in thromboembolic complications in patients with liver cirrhosis in the past decade as a result of an increase in the use of thromboprophylaxis. The lack of specific guidelines for cirrhotic patients is because of the perceived risk of bleeding complications, owing to potential abnormal coagulation laboratory tests and the concomitant presence of risk of portal hypertensive bleeding. Cirrhosis is thus considered to be a relative contraindication for thrombophrophylaxis by some centres. In the largest series that reported on the use of anticoagulation in patients with PVT and liver cirrhosis, Francoz *et al.* described 19 patients on the waiting list for liver transplantation who underwent anticoagulation therapy, obtaining recanalization in 42% without additional bleeding complications.[32] However, only four patients had advanced liver disease (Child C), and the severity of the portal hypertension was not well described by the authors.

Garcia-Fuster and co-workers described the need for anticoagulation in treating DVT in 17 patients with liver cirrhosis.[21] Eleven out of 17 were treated with LWMH, and the remaining six started with LWMH and switched to acenocoumarol thereafter. There was an 83% incidence of bleeding amongst which 35% needed transfusion and only three patients were able to complete the treatment by 3 months. The grade and severity of portal hypertension was not reported by the authors. We treated 38 cirrhotic patients with portal vein thrombosis (12 Child C, 20 Child B and 6 Child A) with LMWH, independent of coagulation parameters, tailoring the LMWH dose according to platelet count. There were two bleeding complications; one variceal bleed from non-high-risk oesophageal varices and one intracranial haemorrhage which was self-limited in a patient older than 60 years with no additional risk factors for bleeding.[33]

Current American College of Chest Physicians (ACCP) guidelines for thromboprophylaxis in patients with important risk factors for bleedings state: 'for medical patients with risk factors for VTE, and for whom there is a contraindication to anticoagulant thromboprophylaxis, we recommend the optimal use of mechanical thromboprophylaxis with graduated compression stockings or intermittent pneumatic compression'.[31] The statement has the maximum grade of evidence and strength of recommendation, therefore it should be considered in cirrhotic patients with high-risk varices.

One disadvantage of the use of LMWH and fondaparinux in patients with cirrhosis, is the unpredictable efficacy, as these drugs require antithrombin to exert its anticoagulant function, and antithrombin levels are frequently decreased in these patients. The use of the new incoming antithrombotic agents, directly inhibiting factor (F)Xa or thrombin, will need very careful evaluation in this subset of patients due to the risk of haemorrhagic complications. The FXa inhibitors rivaroxaban and apixaban are metabolized in the liver and they are contraindicated in severe hepatic diseases because their metabolic inactivation is impaired. Metabolic conversion of the prodrug dabigatran etexilate to dabigatran, a thrombin inhibitor, is completed in the liver and followed by partial biliary excretion of a conjugated derivate. Idraparinux, an antithrombin dependent FXa inhibitor, has no hepatic clearance, but its long half-life (approximately 80 h) and the lack of antidote do represent major problems if bleeding occurs. Finally, all these drugs must be used with caution or are contraindicated in the presence of renal failure.

Conclusions

Nowadays, patients with cirrhosis and liver disease cannot be considered as auto-anticoagulated, because of the clear evidence of the occurrence of thrombotic events with an appreciable incidence of DVT and PE not different from other chronic diseases, despite abnormal standard coagulation tests. The natural reset of the haemostatic balance to a lower level can be easily disturbed by both prohaemorrhagic and prothrombotic conditions. In particu-

lar, patients with liver cirrhosis share the same risk factors for thrombosis as the general population, with orthopaedic surgery, liver resection and immobilization being the most represented precipitating conditions.

Therefore, thromboprophylaxis should be recommended in patients with liver cirrhosis at least when exposed to high-risk conditions for thrombotic complications. LWMHs seem to be relatively safe in this group of patients, however, when important risk factors for bleeding are present, graduated compression stockings or intermittent pneumatic compression should be considered.

Conflicts of interest

None declared.

References

1. Lisman T, Leebeek FW, de Groot PG. (2002) Haemostatic abnormalities in patients with liver disease. *J Hepatol* 37:280–287.
2. Senzolo M, Burra P, Cholongitas E, Burroughs AK. (2006) New insights into the coagulopathy of liver disease and liver transplantation. *World J Gastroenterol* 12:7725–7736.
3. Rapaport SI. (2000) Coagulation problems in liver disease. *Blood Coagul Fibrinolysis* 11 (Suppl. 1):S69–S74.
4. Tripodi A, Salerno F, Chantarangkul V, Clerici M, Cazzaniga M, Primignani M *et al.* (2005) Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests. *Hepatology* 41:553–558.
5. Senzolo M, Burroughs AK. (2007) Hemostasis alterations in liver disease and liver transplantation. In: Kitchens G, Alving B, Kessler G, eds. *Consultative* Hemostasis *and Thrombosis*. Philadelphia, PA: Saunders, pp. 490, 502.
6. Northup PG. (2009) Hypercoagulation in liver disease. *Clin Liver Dis* 13:109–116.
7. Fimognari FL, Violi F. (2008) Portal vein thrombosis in liver cirrhosis. *Intern Emerg Med* 3:213–218.
8. Denninger MH, Chait Y, Casadevall N, Hillaire S, Guillin MC, Bezeaud A *et al.* (2000) Cause of portal or hepatic venous thrombosis in adults: the role of multiple concurrent factors. *Hepatology* 31:587–591.
9. Amitrano L, Brancaccio V, Guardascione MA, Margaglione M, Sacco M, Martino R *et al.* (2002) Portal vein thrombosis after variceal endoscopic sclerotherapy in cirrhotic patients: role of genetic thrombophilia. *Endoscopy* 34:535–538.
10. Wanless IR, Wong F, Blendis LM, Greig P, Heathcote EJ, Levy G. (1995) Hepatic and portal vein thrombosis in cirrhosis: possible role in development of parenchymal extinction and portal hypertension. *Hepatology* 21:1238–1247.
11. Wanless IR, Liu JJ, Butany J. (1995) Role of thrombosis in the pathogenesis of congestive hepatic fibrosis (cardiac cirrhosis). *Hepatology* 21:1232–1237.
12. Budhiraja R, Tuder RM, Hassoun PM. (2004) Endothelial dysfunction in pulmonary hypertension. *Circulation* 109:159–165.
13. Northup PG, McMahon MM, Ruhl AP, Altschuler SE, Volk-Bednarz A, Caldwell SH *et al.* (2006) Coagulopathy does not fully protect hospitalized cirrhosis patients from peripheral venous thromboembolism. *Am J Gastroenterol* 101:1524–1528.
14. Tripodi A, Primignani M, Chantarangkul V, Clerici M, Dell'era A, Fabris F *et al.* (2006) Thrombin generation in patients with cirrhosis: the role of platelets. *Hepatology* 44:440–445.
15. Tripodi A, Primignani M, Chantarangkul V, Viscardi Y, Dell'era A, Fabris FM *et al.* (2009) The coagulopathy of cirrhosis assessed by thromboelastometry and its correlation with conventional coagulation parameters. *Thromb Res* 124:132–136.
16. Tripodi A, Chantarangkul V, Primignani M, Fabris F, Dell'era A, Sei C *et al.* (2007) The international normalized ratio calibrated for cirrhosis (INR-(liver)) normalizes prothrombin time results for model for end-stage liver disease calculation. *Hepatology* 46:520–527.
17. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ *et al.* (2000) Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. *Arch Intern Med* 160:809–815.
18. Huerta C, Johansson S, Wallander MA, Garcia Rodriguez LA. (2007) Risk factors and short-term mortality of venous thromboembolism diagnosed in the primary care setting in the United Kingdom. *Arch Intern Med* 167:935–943.
19. Sogaard KK, Horvath-Puho E, Gronbaek H, Jepsen P, Vilstrup H, Sorensen HT. (2009) Risk of venous thromboembolism in patients with liver disease: a nationwide population-based case-control study. *Am J Gastroenterol* 104:96–101.
20. Gulley D, Teal E, Suvannasankha A, Chalasani N, Liangpunsakul S. (2008) Deep vein thrombosis and pulmonary embolism in cirrhosis patients. *Dig Dis Sci* 53:3012–3017.
21. Garcia-Fuster MJ, Abdilla N, Fabia MJ, Fernandez C, Oliver V, Forner MJ. (2008) [Venous thromboembolism and liver cirrhosis]. *Rev Esp Enferm Dig* 100:259–262.
22. Webster GJ, Burroughs AK, Riordan SM. (2005) Review article: portal vein thrombosis – new insights into aetiology and management. *Aliment Pharmacol Ther* 21:1–9.
23. Ben Ari Z, Panagou M, Patch D, Bates S, Osman E, Pasi J *et al.* (1997) Hypercoagulability in patients with primary biliary cirrhosis and primary sclerosing cholangitis evaluated by thrombelastography. *J Hepatol* 26:554–559.
24. Segal H, Cottam S, Potter D, Hunt BJ. (1997) Coagulation and fibrinolysis in primary biliary cirrhosis compared with other liver disease and during orthotopic liver transplantation. *Hepatology* 25:683–688.
25. Pihusch R, Rank A, Gohring P, Pihusch M, Hiller E, Beuers U. (2002) Platelet function rather than plasmatic coagulation explains hypercoagulable state in cholestatic liver disease. *J Hepatol* 37:548–555.
26. Nieuwdorp M, Stroes ES, Meijers JC, Buller H. (2005) Hypercoagulability in the metabolic syndrome. *Curr Opin Pharmacol* 5:155–159.
27. Yudkin JS, Juhan-Vague I, Hawe E, Humphries SE, di MG, Margaglione M *et al.* (2004) Low-grade inflammation may play a role in the etiology of the metabolic syndrome in patients with coronary heart disease: the HIFMECH study. *Metabolism* 53:852–857.
28. Samonakis DN, Koutroubakis IE, Sfiridaki A, Malliaraki N, Antoniou P, Romanos J *et al.* (2004) Hypercoagulable states in patients with hepatocellular carcinoma. *Dig Dis Sci* 49:854–858.
29. Cerutti E, Stratta C, Romagnoli R, Schellino MM, Skurzak S, Rizzetto M *et al.* (2004) Thromboelastogram monitoring in the perioperative period of hepatectomy for adult living liver donation. *Liver Transpl* 10:289–294.
30. Tsuji K, Eguchi Y, Kodama M. (1996) Postoperative hypercoagulable state followed by hyperfibrinolysis related to wound healing after hepatic resection. *J Am Coll Surg* 183:230–238.
31. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR

et al. (2008) Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). *Chest* 133 (6 Suppl.):381S–453S.

32. Francoz C, Belghiti J, Vilgrain V, Sommacale D, Paradis V, Condat B *et al.* (2005) Splanchnic vein thrombosis in candidates for liver transplantation: usefulness of screening and anticoagulation. *Gut* 54:691–697.

33. Senzolo M, Ferronato C, Burra P, Sartori MT. (2009) Anticoagulation for portal vein thrombosis in cirrhotic patients should be always considered. *Intern Emerg Med* 4:161–162; author reply, 163–164.